

PCT

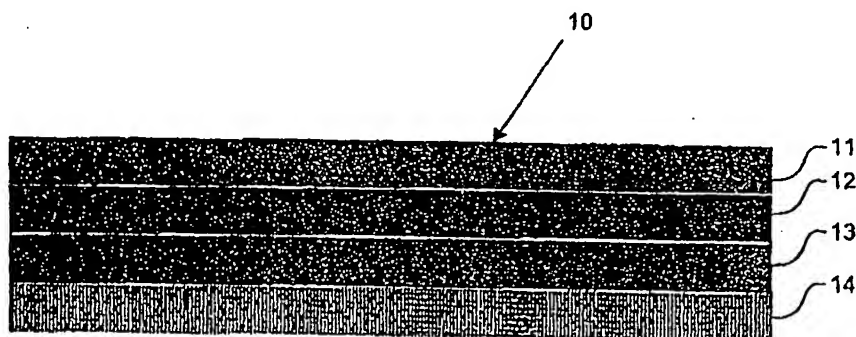
WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : A61K 9/00	A2	(11) International Publication Number: WO 00/33812 (43) International Publication Date: 15 June 2000 (15.06.00)
(21) International Application Number: PCT/US99/28697 (22) International Filing Date: 7 December 1999 (07.12.99) (30) Priority Data: 60/111,285 7 December 1998 (07.12.98) US (71) Applicant (for all designated States except US): ELAN CORPORATION, PLC [IE/IE]; Lincoln House, Lincoln Place, 2 Dublin (IE). (72) Inventors; and (75) Inventors/Applicants (for US only): MIRANDA, J. [US/US]; Elan Transdermal Technologies, 3250 Commerce Parkway, Miramar, FL 33025 (US). BETLACH, C., J., II [US/US]; Elan Transdermal Technologies, 3250 Commerce Parkway, Miramar, FL 33025 (US). (74) Agents: BEARD, Collen, A. et al.; Jones & Askew, LLP, 2400 Monarch Tower, 3424 Peachtree Road, N.E., Atlanta, GA 30326 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  Published Without international search report and to be republished upon receipt of that report.

(54) Title: TRANSDERMAL PATCH FOR DELIVERING VOLATILE LIQUID DRUGS



(57) Abstract

A transdermal patch for administering a volatile liquid drug, such as nicotine, transdermally to a patient comprising a four-layer laminated composite of: a top drug impermeable backing layer; a pressure sensitive silicone adhesive layer containing the drug; a pressure sensitive acrylic adhesive layer also containing the drug; and a removable siliconized release liner layer. Also disclosed is a method for treating a person for nicotine dependence and particularly for treating a woman for nicotine dependence.

BEST AVAILABLE COPY

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## TRANSDERMAL PATCH FOR DELIVERING VOLATILE LIQUID DRUGS

### TECHNICAL FIELD

5 This invention is in the field of transdermal drug delivery devices. More particularly, it relates to a method for making transdermal patches that deliver volatile liquid drugs, such as nicotine, mecamylamine and selegiline, and to the resulting patches. The invention also relates to a method for treating a person for nicotine dependence comprising transdermally administering an effective amount of mecamylamine to the person without transdermal coadministration of nicotine. The invention further relates to a method for treating women for  
10 nicotine dependence comprising transdermally co-administering effective doses of mecamylamine and nicotine.

### BACKGROUND ART

15 There are two basic types of transdermal patches that are used to deliver liquid drugs. One is a liquid reservoir patch in which the liquid drug, either neat or dissolved in a carrier, is confined in a pouch or sac within the device. An example of such a device for delivering nicotine is shown in Fig. 1 of U.S. Pat. No. 5,364,630. The other is a matrix patch in which the liquid drug is dissolved in one or more polymeric layers of a laminated composite. Examples of  
20 matrix patches that deliver nicotine are described in U.S. Pat. No. 5,603,947. The present invention relates to a matrix patch.

25 In the manufacture of matrix patches for administering volatile liquid drugs such as nicotine it is common to attempt to avoid steps involving heat treatment, e.g., drying, so as to avoid excessive loss or degradation of the drug. For instance U.S. Pat. No. 4,915,950 and 5,603,947 describe a printing procedure whereby neat nicotine is applied to a nonwoven fabric laminated to a polyisobutylene adhesive layer. Alternatively "hot" melt adhesives that melt at relatively low temperatures have been used as a matrix material for these drugs. See U.S. Pat. No. 5,411,739.

30 PCT Pub. No. WO 96/40085 describes transdermal matrix patches for administering drugs such as selegiline, nitroglycerin and nicotine, that are liquid at normal room temperature. The publication suggests making a monolithic matrix of the drug in an adhesive by mixing one

or more polymeric adhesives, preferably polyacrylate and polysiloxane, and the drug in a volatile solvent, casting the mixture, and evaporating the solvent. The publication lists as examples of volatile solvents isopropanol, ethanol, xylene, toluene, hexane, cyclohexane, heptane, ethyl acetate and butyl acetate.

5

When silicone adhesives have been used as the matrix material in nicotine patches the matrix layer has been cast from a heptane solution. See, for instance, Example 1 of U.S. Pat. No. 5,603,947. Other co-solvents, including hexane, have been suggested for use with silicone adhesives used in transdermal devices. See p. 3, line 51, et seq. of EPO 524776 A1.

10

Mecamylamine is an antagonist to nicotine. U.S. Patent Nos. 5,316,759, 5,726,190, and 5,574,052 teach the coadministration of mecamylamine and nicotine to treat nicotine dependency. These patents do not teach or suggest the transdermal administration of mecamylamine itself to treat nicotine dependency. Furthermore, the prior art does not teach that coadministration of mecamylamine and nicotine is especially effective as a smoking cessation aid specifically suited for women.

15

#### DISCLOSURE OF THE INVENTION

20

One aspect of this invention is a transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

- a) a top backing layer that is impermeable to the drug;
- b) silicone adhesive layer containing the drug and underlying the backing layer;
- c) an acrylic adhesive layer also containing the drug that underlies and is in diffusional contact with the silicone adhesive layer; and
- d) a removable release liner layer underlying the acrylic adhesive layer, wherein the combined amount of drug in the silicone adhesive layer and the acrylic adhesive layer is sufficient to provide a therapeutically effective amount of drug to the patient.

25

30

Another aspect of the invention is a method of making a transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

- a) coating a solution of the drug and a silicone adhesive in hexane onto a backing layer;
- b) evaporating the hexane from the coating to form a silicone adhesive layer containing the drug; and

c) laminating a polyacrylate adhesive layer affixed to a release liner layer onto the silicone adhesive layer such that the silicone adhesive layer and the acrylic adhesive layer are in diffusional contact with each other.

5 Another aspect of the invention is a method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine without transdermal coadministration (or other coadministration except by smoking) of nicotine to the person.

10 A further aspect of the invention is a method for treating a woman for nicotine dependence comprising transdermally coadministering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine.

#### BRIEF DESCRIPTION OF THE DRAWINGS

15

Figure 1 is a elevational cross-sectional view of an embodiment of the invention patch.

Figures 2-6 are graphs of the results of the *in vitro* skin flux tests described in the examples.

20

Figures 7 and 8 are graphs of the results of the clinical studies described in the examples.

#### MODES FOR CARRYING OUT THE INVENTION

25

As used herein the term "volatile liquid drug" intends a drug that (i) is capable of permeating through unbroken human skin at therapeutically effective rates from a patch of practical size, the permeation either being unenhanced or enhanced through coadministration of one or more skin permeation enhancing agents, (ii) is a liquid at 25°C, atmospheric pressure, and (iii) has a boiling point less than about 300°C at atmospheric pressure. Examples of such drugs

30

are nicotine, mecamylamine, selegiline, and nitroglycerine.

As used herein the term "diffusional contact" intends a relationship, either through direct contact or through indirect contact via an intermediary material, between two surfaces or layers such that drug is able to pass by diffusion from one surface or layer to the other surface or layer.

As used herein the term "treating a person for nicotine dependence" intends causing the person to reduce or eliminate his or her intake of nicotine from smoking and/or chewing tobacco on a temporary or permanent basis.

5

The embodiment of the invention shown in Figure 1 is a four-layer laminated composite matrix type transdermal patch, generally designated 10. The four layers are: (1) a top drug-impermeable backing layer 11; (2) an intermediate drug-containing silicone adhesive layer 12; (3) a basal drug-containing polyacrylic adhesive layer 13; and (4) a removable release liner layer 14.

10

Materials for making backing layer 11 are well known in the art. They include various polymers such as polyethylene terephthalate, polyethylene, polypropylene and polyvinyl chloride, metal foils such as aluminum foil, and polymer-metal composites.

15

Adhesive layer 12 is made from a pressure sensitive silicone adhesive. An amine compatible silicone adhesive is preferred for use with drugs, such as nicotine, which contain amine groups. These adhesives are described in detail in the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition, pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989). See also Pfister, W.R., et al. "Silicon Adhesives for Transdermal Drug Delivery" Chemistry in Britain (Jan. 1991), pp. 43-46 and EP Pub. No. 0524776 A1. Suitable commercially available silicone pressure sensitive adhesives are available from Dow Corning under the trademark BIO-PSA. The silicone pressure sensitive adhesives are supplied commercially as solutions in a solvent. Per the present invention the solvent should be hexane. The thickness of layer 12 will usually be in the range of about 25 to 100 microns, more usually 50 to 75 microns. Expressed alternatively, the layer 12 will be present at about 4 to 18 mg/cm<sup>2</sup>, more usually 8 to 14 mg/cm<sup>2</sup>. Adhesive layer 12 initially (before it is laminated to adhesive layer 13) contains the entire drug loading. In this regard, the drug(s) will usually be added to the silicone adhesive in amounts ranging between about 5% to 50% by weight, more usually 10% to 30% by weight, based on the total dry weight of drug and adhesive.

20

25

30

Adhesive layer 13 is made from one or more solution acrylic pressure sensitive adhesives. These adhesives are described in detail in the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition, pp. 396-456 (D. Satas, ed.) Van Nostrand Reinhold, New

York (1989). They are usually copolymers composed of: 50% to 90% of a main acrylate or methacrylate monomer, usually 2-ethylhexyl acrylate, butylacrylate, or iso-octyl acrylate; 10% to 40% of a modifying monomer such as vinyl acetate; and 2% to 20% of a functional group-containing monomer such as acrylic acid. Examples of suitable commercially available solution acrylic pressure sensitive adhesives are: National Starch DuroTak® adhesives 87-2194 and 87-2070. The thickness of the acrylic adhesive layer 13 will usually be about the same as that of layer 12. After lamination to the silicone adhesive layer 12 and equilibration of the drug between layers 12 and 13, layer 13 will also contain drug. In this regard the drug will usually constitute about 2.5% to 30% by weight, preferably 5% to 15% by weight, of layer 13 after equilibration occurs.

The release liner layer 14 is removed before device 10 is placed on the skin. After layer 14 is removed the lower surface of layer 13 is exposed and defines the basal surface of the device which is intended to be placed directly in contact with the skin. Release liner layers are well known in the transdermal patch art. They are made of materials that permit the layer to be easily stripped or peeled away from the adjacent pressure sensitive adhesive layer. Release liner layers are typically made from drug impermeable polymers such as polyesters which are coated with materials such as silicone or fluorinated hydrocarbons that reduce the adhesiveness between it and the adjacent pressure sensitive adhesive layer. In this regard since the acrylic pressure sensitive adhesive layer rather than the silicone pressure sensitive adhesive layer defines the basal surface of the device it is possible to use a siliconized release liner. Such liners are generally not compatible with silicone adhesives. Siliconized liners are more economical than fluorocarbon coated liners. Further, use of the acrylic pressure sensitive adhesive as the basal layer provides a more controlled and predetermined delivery of the drug than could be achieved using a silicone adhesive basal layer. The particular drug release profile from the patch can be varied by altering the thickness and/or composition of the acrylic pressure sensitive adhesive layer and/or the drug loading, and/or by employing a permeation enhancer.

The drug is released from the surface of the acrylic pressure sensitive adhesive to the skin at a therapeutically effective rate. That rate will depend upon the particular drug. In the case of nicotine, the rate will usually be in the range of 0.2 to 1.5 mg/hr, preferably 0.3 to 0.9 mg/hr. In the case of co-administration of nicotine and the mecamylamine, the nicotine rate will usually be in the range of 0.2 to 1.5 mg/hr, preferably 0.3 to 0.9 mg/hr, and the mecamylamine rate will usually be in the range of 0.02 to 1 mg/hr, preferably 0.1 to 0.6 mg/hr. In the case of

mecamylamine alone, the rate will usually be in the range of 0.02 to 1 mg/hr, preferably 0.1 to 0.6 mg/hr. In the case of selegiline, the rate will usually be in the range of 0.2 to 3 mg/day. The flux (rate per unit area) of drug from the basal surface of the acrylic pressure sensitive adhesive and the area of that surface are matched to provide the desired rate of drug administration. As indicated, the flux may be varied by altering the drug loading, composition and/or thickness of the acrylic pressure sensitive adhesive layer, and/or by the use of permeation enhancers. The surface area of the layer in diffusional contact with the skin will usually be in the range of 5 to 100 cm<sup>2</sup>, more usually in the range of about 10 to 50 cm<sup>2</sup>. Each patch may be applied to the skin for periods of from several hours up to about a week, and more preferably for about 1 to 3 days.

The patches of the invention are made in the following manner. The drug(s) is dissolved in the desired proportion(s) in a hexane solution of the pressure sensitive silicone adhesive. The drug(s) will normally constitute about 2.5% to 25% by weight of the solution. This solution is then cast onto the backing layer and allowed to dry. By casting the drug and silicone adhesive from a hexane solution, very low casting and drying temperatures (30°C to 40°C) may be used, thus reducing degradation or loss of the liquid drug(s) during the casting and drying process. Even though low processing temperatures in the 30°C to 40°C range are used, low residual hexane levels (e.g., < 0.1 % by wt.) are found in the layer after about 1 to 5 min. of drying. Other solvents, such as heptane and toluene, are not suitable since they require higher processing temperatures and thus result in more drug degradation and/or evaporation during coating and drying. Other pressure sensitive adhesives such as acrylics or polyisobutylenes are similarly not suitable for formulating liquid drugs since they require higher processing temperatures to remove their solvents (e.g., ethyl acetate, heptane, etc.). The silicone adhesive also has excellent adhesion to the backing. A solution of the acrylic pressure sensitive adhesive is cast onto a siliconized release liner layer and permitted to dry. The acrylic pressure sensitive adhesive/release liner subassembly is then laminated to the drug-containing silicone pressure sensitive adhesive/backing subassembly to form the final laminated composite. After lamination the drug(s) equilibrates in the adjacent adhesive layers. Patches are cut/punched from the composite and placed in appropriate packaging.

Alternatively, the drug and silicone adhesive solution can be cast onto a disposable liner and dried as described. The sub-assembly can be laminated to the acrylic pressure sensitive adhesive/release liner subassembly. The disposable liner is then removed to expose the top surface of the silicone adhesive layer. A backing is then laminated to the top surface of the



silicone adhesive layer to form the final laminated composite. In still another alternative manufacturing scheme, the solution of silicone adhesive and drug is cast directly into the acrylic pressure sensitive adhesive:release liner subassembly and dried. A backing is then applied to form the completed laminated composite.

5

It has surprisingly been found that, in the treatment of nicotine dependence, women respond more favorably to a patch that combines nicotine and mecamylamine than to a patch that contains either nicotine or mecamylamine alone. The patch can be administered while the woman continues to smoke and then ceases smoking or if she chooses to stop smoking at the same time as beginning treatment.

10

For treatment of nicotine dependence, the patches of the invention are typically worn for a total period of about 3 to 16 weeks. During the first 1 to 4 weeks, preferably 2 to 3 weeks, the patient is allowed to smoke as desired. During the remainder of the treatment, i.e., two to 12 weeks, preferably 4 to 8 weeks, the patient is advised to not smoke.

15

### EXAMPLES

The following examples further illustrate the patches of the invention and the process used to make them. These examples are not intended to limit the invention in any manner.

20

#### Example 1: Preparation and Testing of Nicotine Patch

Nicotine was added to a hexane solution of Dow Corning BIO-PSA amine-compatible silicone pressure sensitive adhesive to a level of approximately 12% by weight based on the combined dry weight of adhesive and nicotine. The resulting hexane solution of adhesive and nicotine was coated onto a 3M Scotchpak 1109 polyester/polyolefin backing at 13.8 mg/cm<sup>2</sup> (1.63 mg/cm<sup>2</sup> nicotine and 12.17 mg/cm<sup>2</sup> adhesive) and the coated backing was dried at 30°C to 40°C for about 3 min.

25

National Starch DuroTak 87 2194 acrylic solution pressure sensitive adhesive was coated onto a 125 micron thick Daubert Coater Products 1-5 PESTR (Matte) - 164Z siliconized polyester release liner at 13.18 mg/cm<sup>2</sup> and the coated release liner was dried at 100°C for about 10 min.

30

The dried silicone adhesive/nicotine-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the nicotine distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of nicotine within the layers was about 6% (w/w) after equilibration.

In vitro nicotine flux from the laminated composite was determined at 32°C through human cadaver epidermis into an infinite sink using modified Franz glass diffusion cells. Nicotine assays were made by HPLC.

For comparison purposes the flux of nicotine from commercial Habitrol3 21 mg/day patches was determined using the same test procedure. Figure 2 is a graph of the nicotine flux from the composite of the example and from the Habitrol3 patches versus time.

#### Example 2: Preparation and Testing of Nicotine/Mecamylamine Patches

Nicotine and mecamylamine were added to a hexane solution of Dow Corning BIO-PSA amine compatible silicone pressure sensitive adhesive. Two batches were made: one contained approximately 10% nicotine and 6.4% mecamylamine based on the total dry weight of the adhesive and the two drugs; and a second contained approximately 10% nicotine and 4.2% mecamylamine, based on the total dry weight of the adhesive and the two drugs. The batches were separately coated onto a 3M Scotchpak 1109 polyester/polyoefin backing film at 9.6 mg/cm<sup>2</sup> (0.96 mg/cm<sup>2</sup> nicotine, 0.61 mg/cm<sup>2</sup> mecamylamine, 8.03 mg/cm<sup>2</sup> adhesive for the first batch; 0.96 mg/cm<sup>2</sup> nicotine, 0.40 mg/cm<sup>2</sup> mecamylamine, 8.24 mg/cm<sup>2</sup> adhesive for the second batch) and then dried at 30 to 40°C for about 2 min.

A blend of two National Starch DuroTak acrylic solution polymers, 87-2196 and 87-2516, 25% and 75% w/w, respectively, was made. The blend was coated at 8.0 mg/cm<sup>2</sup> onto a 75 micron thick Daubert Coater Products siliconized polyester release liner (1-3 PESTR (Matte) - 164Z) and dried at about 100°C for about 10 min.

The drug-containing silicone adhesive/backing subassembly was then laminated to the acrylic adhesive/release liner subassembly to form a four layer/laminated composite. After lamination the nicotine and mecamylamine distributed themselves uniformly within the adjacent

adhesive layers. The concentration of the drugs in the adhesive layers after equilibration was: nicotine, 5.45% (w/w) and mecamlamine 3.47% (w/w) for the composite made from the first batch and 5.45% (w/w) and 2.27% (w/w), respectively, for the composite made from the second batch. Patches about 23 cm<sup>2</sup> in area were cut from the composites. These patches were designed to deliver 21 mg of nicotine and 6 mg of mecamlamine in 24 hr and 21 mg of nicotine and 3 mg of mecamlamine in 24 hr, respectively.

Nicotine and mecamlamine fluxes from the patches were determined using the procedure described Example 1. Mecamlamine assays were made by GC. Figure 3 is a graph showing the nicotine flux from the patches versus time. Patches made from the first batch composite are designated 21/6; those from the second batch composite are designated 21/3. Figure 4 similarly is a graph showing the mecamlamine flux from the patches.

#### Example 3 Preparation and Testing of Selegiline Patch

Selegiline was added to a hexane solution of Dow Corning BIO-PSA® amine-compatible silicone pressure sensitive adhesive to a concentration of approximately 10% by weight based on the combined dry weight of adhesive and selegiline. The resulting hexane solution of adhesive and selegiline was coated on 3M Scotchpak 1109 polyester/polyolefin backing at 10.0 mg/cm<sup>2</sup> (1.0 mg/cm<sup>2</sup> selegiline and 9.0 mg/cm<sup>2</sup> adhesive) and the coated backing was dried at 30°C to 40°C for about 3 minutes.

National Starch DuroTak® 87-2194 acrylic solution pressure sensitive adhesive was coated onto a 125 micron thick Daubert Coated Products 1-5 PESTER (Matte)-164Z siliconized polyester release liner at 8.0 mg/cm<sup>2</sup> and the coated release liner was dried at about 100°C for about 10 minutes.

The dried silicone adhesive/selegiline-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the selegiline distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of selegiline within the layers is about 5.5% (w/w) after equilibration.

Selegiline flux from the patches was determined using the procedure described in Example 1. Selegiline assays were made by HPLC.

Figure 5 is a graph of the selegiline flux from the composite of this example versus time.

5

Example 4. Preparation and Testing of Mecamylamine Patch

Mecamylamine was added to a hexane solution of Dow Corning BIO-PSA® amine-compatible silicone pressure sensitive adhesive to a concentration of approximately 6.3% by weight based on the combined dry weight of adhesive and mecamylamine. The resulting hexane  
10 solution of adhesive and mecamylamine was coated on 3M Scotchpack 1109 polyester/polyolefin backing at 9.6 mg/cm<sup>2</sup> (0.61 mg/cm<sup>2</sup> mecamylamine and 8.99 mg/cm<sup>2</sup> adhesive) and the coating backed was dried at 30°C to 40°C for about 3 minutes.

A blend of two National Starch DuroTak® acrylic solution polymers, 87-2196 and 87-2516, 25% and 75% w/w, respectively, was made. The blend was coated onto a 75 micron thick  
15 Daubert Coated Products 1-2 PESTR (Matte)-164Z siliconized polyester release liner at 8.0 mg/cm<sup>2</sup> and the coated release liner was dried at about 100°C for about 10 minutes.

The dried silicone adhesive/mecamylamine-coated backing layer subassembly was then  
20 laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the mecamylamine distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of mecamylamine within the layers is about 3.47% (w/w) after equilibration. Patches about 23 cm<sup>2</sup> in area were cut from the composites. These patches were  
25 designed to deliver 6 mg of mecamylamine in 24 hr.

Mecamylamine flux from the patches was determined using the procedure described in Example 1. The mecamylamine assay was done by gas chromatography. Figure 6 is a graph of  
30 the mecamylamine flux from the composite of this example versus time; mecamylamine flux through the same section of cadaver skin from the 21/3 and 21/6 compositions of Example 2 are shown for comparison.

Study A.

Patches made according to Examples 1, 2 and 4 and a placebo patch were subject to a clinical study. The study was a multi-center, double-blind, randomized parallel group study. Patients were randomized to receive one of five treatments: nicotine/mecamylamine 21/6;  
 5 nicotine/mecamylamine 21/3; nicotine (21 mg/24 hr); mecamylamine (6 mg/24 hr) and placebo. Patches were applied daily for the first six weeks of the study. Patients were instructed to continue smoking for the first two weeks and to stop smoking thereafter.

Among the efficacy parameters monitored during the study were four week continuous  
 10 abstinence after the quit smoking date, nicotine plasma concentration, and ad hoc smoking during the treatment period.

Table 1 below provides the overall abstinence data for the study. In the table "N" represents the number of patients, "No" indicates non-abstinence and "Yes" indicates abstinence.  
 15 As indicated the nicotine/mecamylamine 21/6 gave the highest abstinence.

**Table 1**

	Overall	21/6	21/3	21/0	0/6	Pla
N	705	142	141	141	140	141
No	82%	74%	79%	79%	82%	92%
Yes	18%	26%	21%	21%	18%	8%

Figure 7 is a graph showing the mean nicotine plasma concentrations in ng/ml of the  
 20 patients by treatment and time. As shown, the mecamylamine only patch (0/6) produced a steady decline in nicotine levels even during the initial two-week period of the study. Fig. 8 is a graph showing the mean observed change in the number of cigarettes smoked by treatment and day. Surprisingly, the number of cigarettes smoked did not increase with the mecamylamine  
 25 only (0/6) treatment, as the literature reports that oral mecamylamine administration increased ad hoc cigarette consumption.

Study B.

A second multi-center, double-blind, randomized parallel group clinical study was conducted. Patients were randomized to receive one of three treatments: nicotine/mecamylamine 21/6; nicotine/mecamylamine 21/3, and nicotine (21 mg/24 hr). Patient instructions were the same as in the first study.

The abstinence data for this study are summarized in Table 2. In this study the nicotine/mecamylamine combination was again more effective than nicotine alone.

**Table 2**

Treatment	21/6	21/3	21/0
N	180	180	180
Abstinence	29%	29%	23%

A detailed examination of the data the clinical studies yielded a surprising difference in abstinence rates for females and males. In both studies, the abstinence rate for females in the 21/6 treatment group was 31% compared to the 21/0 treatment group rates of 17% in the first study and 18% in the second study. These gender specific data are summarized in Table 3.

Table 3

Study	Gender		21/6	21/3	21/0	0/6	Plac
First	Female	N	70	67	63	75	74
		% Abst.	31	16	17	17	9
	Male	N	72	74	78	65	67
		% Abst.	21	26	24	18	6
Second	Female	N	93	96	91		
		% Abst.	31	29	18		
	Male	N	87	84	89		
		% Abst.	28	29	28		

N = number of subjects in study.

5 % Abst.= Four-week continuous abstinence results.

10 Modifications of the above described modes for carrying out the invention that are obvious to persons of skill in the transdermal patch art are intended to be within the scope of the following claims. All publications, patent applications and patents noted above are hereby incorporated by reference.

CLAIMS

1. A transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:
- 5           a) a top backing layer that is impermeable to the drug;
- b) an intermediate silicone adhesive layer containing the drug and underlying the backing layer;
- c) an acrylic adhesive layer also containing the drug that underlies and is in diffusional contact with the silicone adhesive layer; and
- 10           d) a removable release liner layer underlying the acrylic adhesive layer, wherein the combined amount of drug in the silicone adhesive layer and acrylic adhesive layer is sufficient to provide a therapeutically effective amount of drug to the patient.
2. The transdermal patch of claim 1, wherein the drug is nicotine and the patch is
- 15           capable of administering 0.2 to 1.5 mg nicotine per hour to the patient.
3. The transdermal patch of claim 1, wherein the drug is a combination of nicotine and mecamylamine and the patch is capable of administering 0.2 to 1.5 mg nicotine per hour and 0.02 to 1 mg mecamylamine per hour to the patient.
- 20           4. The transdermal patch of claim 1 wherein the drug is selegiline and the patch is capable of administering 0.2 to 3 mg selegiline per day to the patient.
5. The patch of claim 1 wherein the drug is mecamylamine only and the patch is capable
- 25           of administering 0.02 to 1 mg mecamylamine per hour to the patient.
6. The patch of claim 1 wherein the release liner layer is a siliconized release liner layer.
7. The patch of claim 1 wherein the acrylic adhesive layer is made from a blend of two
- 30           acrylic adhesives.



8. A method of making a transdermal patch for administering a volatile liquid drug to a patient comprising:

a) coating a solution of the drug and a silicone adhesive in hexane onto a backing layer;

b) evaporating the hexane from the coating to form a layer of drug-containing silicone adhesive on the backing layer; and

c) laminating an assembly comprising an acrylic adhesive coated onto a release liner layer onto the silicone adhesive layer on the backing layer such that the silicone adhesive layer and the acrylic adhesive layer are in diffusional contact with each other.

9. The method of claim 8 wherein step b) is carried out at 30°C to 40°C.

10. The method of claim 8 wherein the release liner layer is a siliconized release liner layer.

11. The method of claim 8 wherein the drug is nicotine.

12. The method of claim 8 wherein the drug is a combination of nicotine and mecamylamine.

13. The method of claim 8 wherein the drug is selegiline.

14. The method of claim 8 wherein the drug is mecamylamine only.

15. A method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine without transdermal co-administration of nicotine to the person.

16. The method of claim 15 wherein the rate of mecamylamine administration is 0.02 to 1 mg/hr.

17. The method of claim 15 wherein the rate of mecamylamine administration is 0.1 to 0.6 mg/hr.

18. A method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine to the person for a first time period during which the person smokes cigarettes as desired and continuing said administration for a second time period during which the person is advised to not smoke.
- 5
19. The method of claim 18 wherein the first time period is about 1 to about 4 weeks and the second time period is about 2 to about 12 weeks.
20. The method of claim 18 wherein the first time period is about 2 to about 3 weeks and the second time period is about 4 to 8 weeks.
- 10
21. A method for treating a woman for nicotine dependence comprising transdermally co-administering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine to the woman.
- 15
22. The method of claim 21 wherein the rate of mecamylamine administration is 0.02 to 1 mg/hr and the rate of nicotine administration is 0.2 to 1.5 mg/hr.
23. The method of claim 21 wherein the rate of mecamylamine administration is 0.1 to 0.6 mg/hr and the rate of nicotine administration is 0.3 to 0.9 mg/hr.
- 20
24. A method for treating a woman for nicotine dependence comprising transdermally co-administering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine to the woman for a first time period during which the woman smokes cigarettes as desired and continuing said administration for a second time period during which the woman is advised to not smoke.
- 25
25. The method of claim 24 wherein the first time period is about 1 to about 4 weeks and the second time period is about 2 to about 12 weeks.
- 30
26. The method of claim 24 wherein the first time period is about 2 to about 3 weeks and the second time period is about 4 to 8 weeks.

1/8

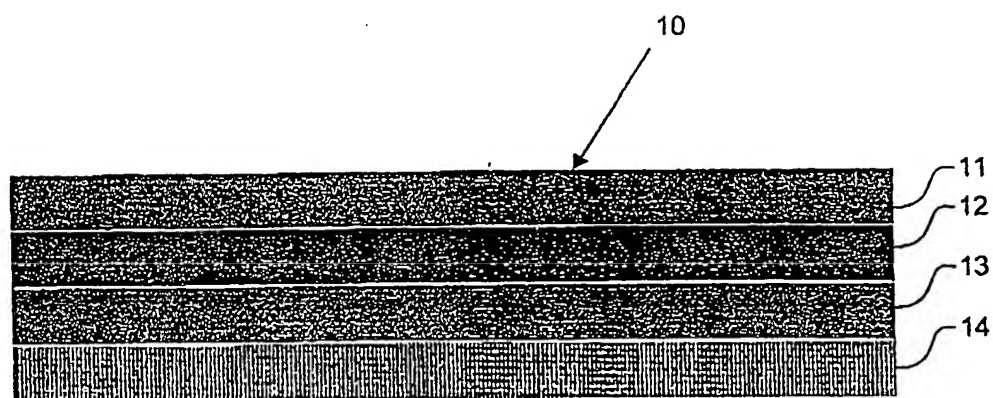


FIGURE 1

2/8

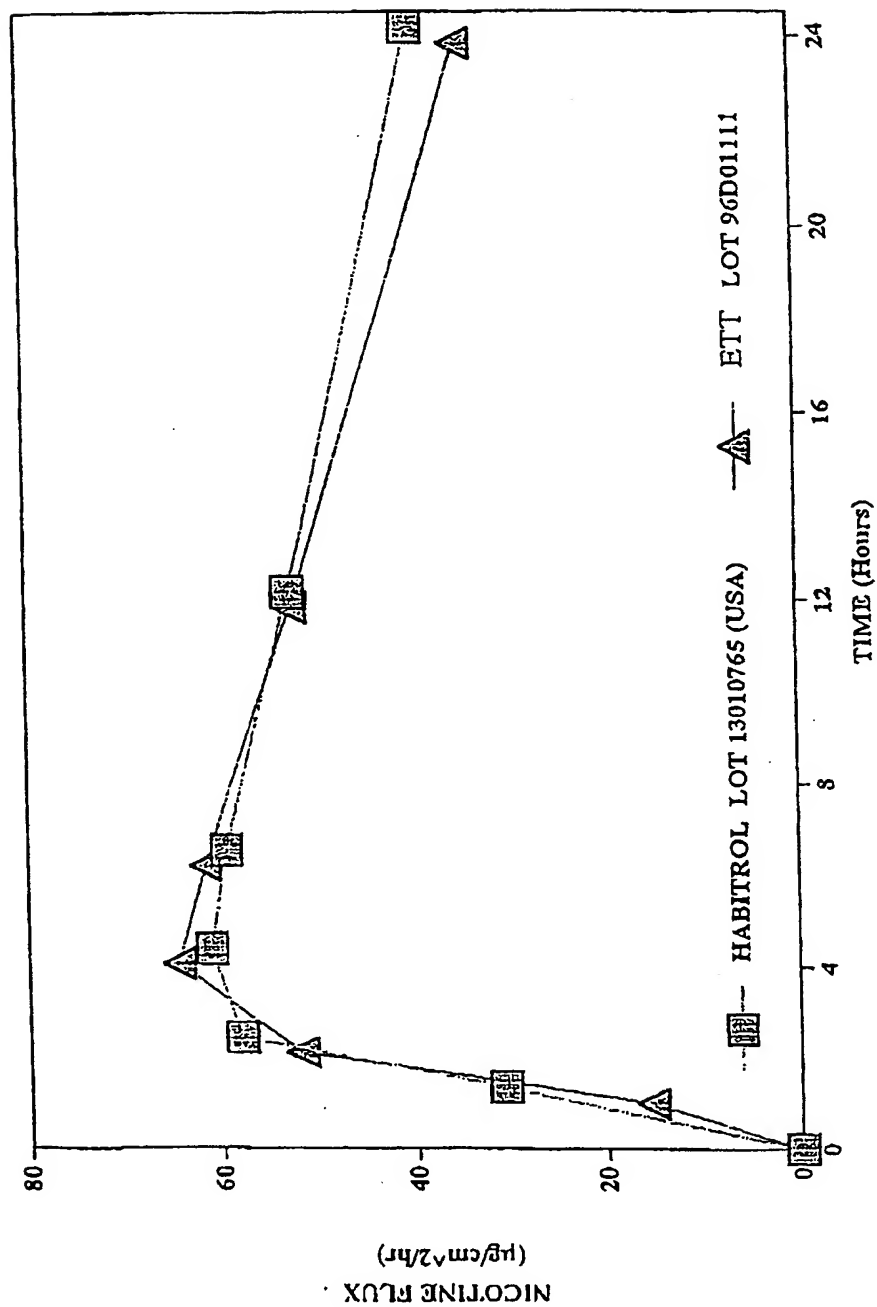


FIGURE 2

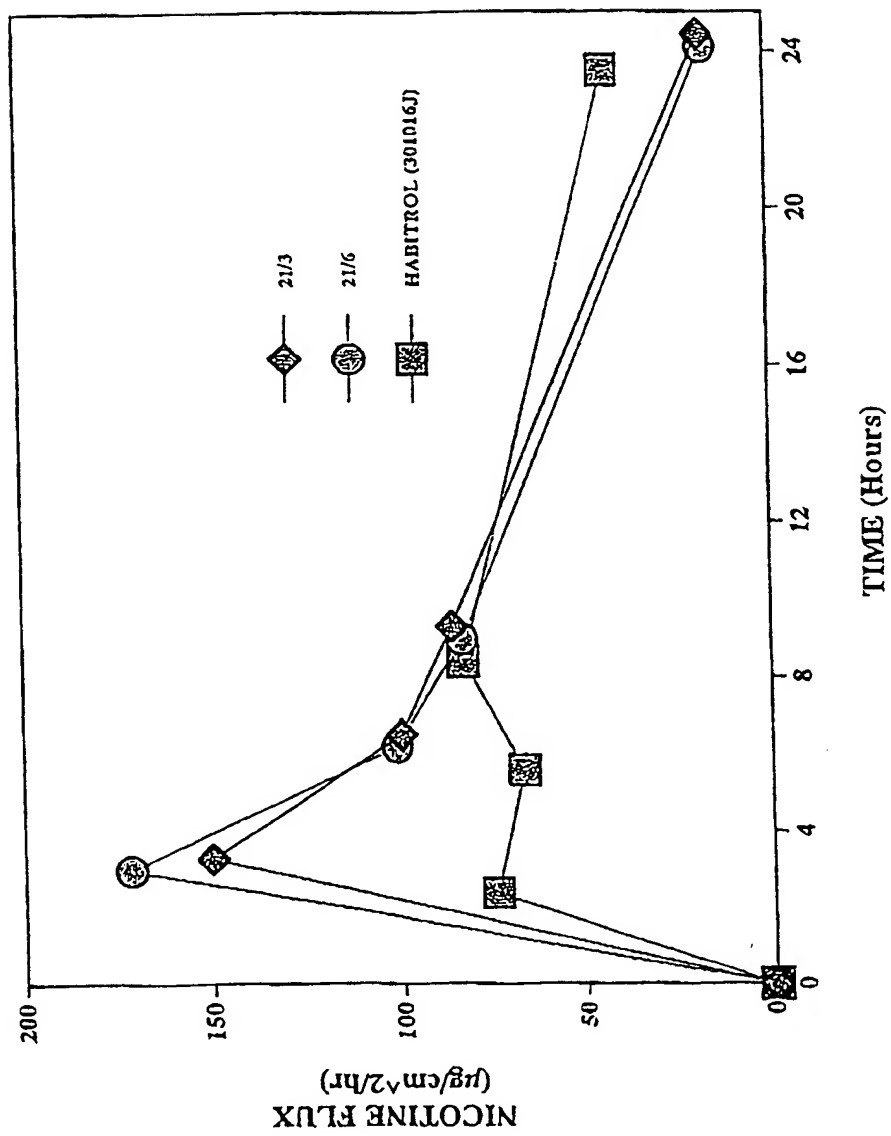


FIGURE 3

4/8

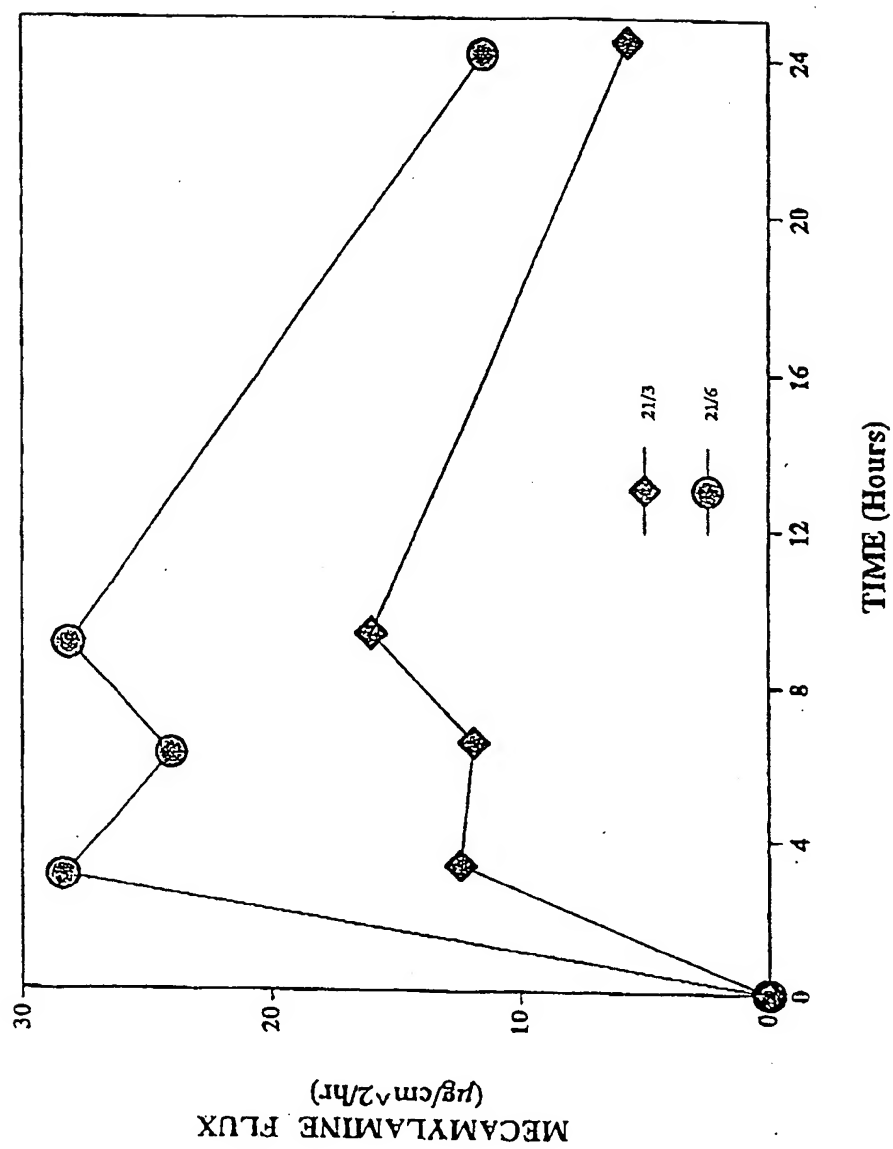


FIGURE 4

5/8

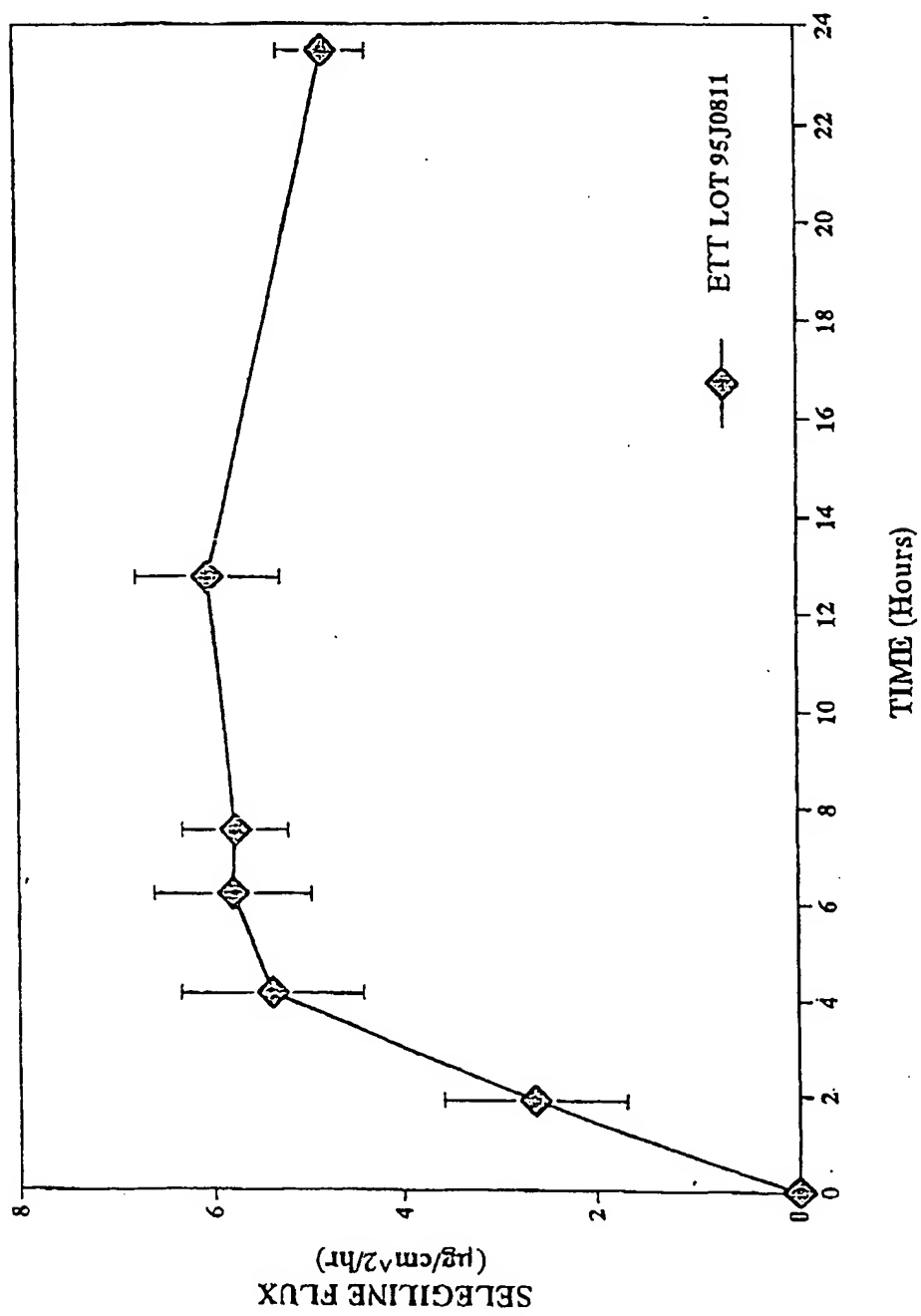


FIGURE 5

6/8

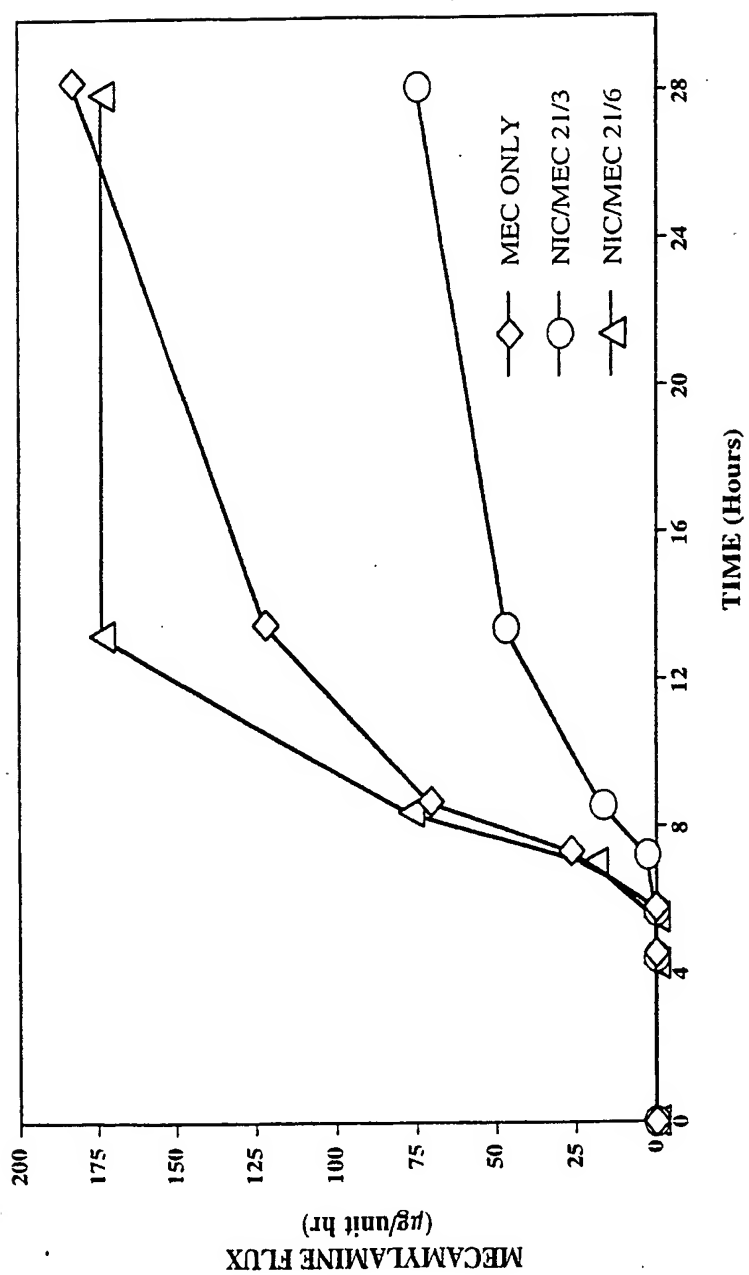


FIGURE 6



7/8

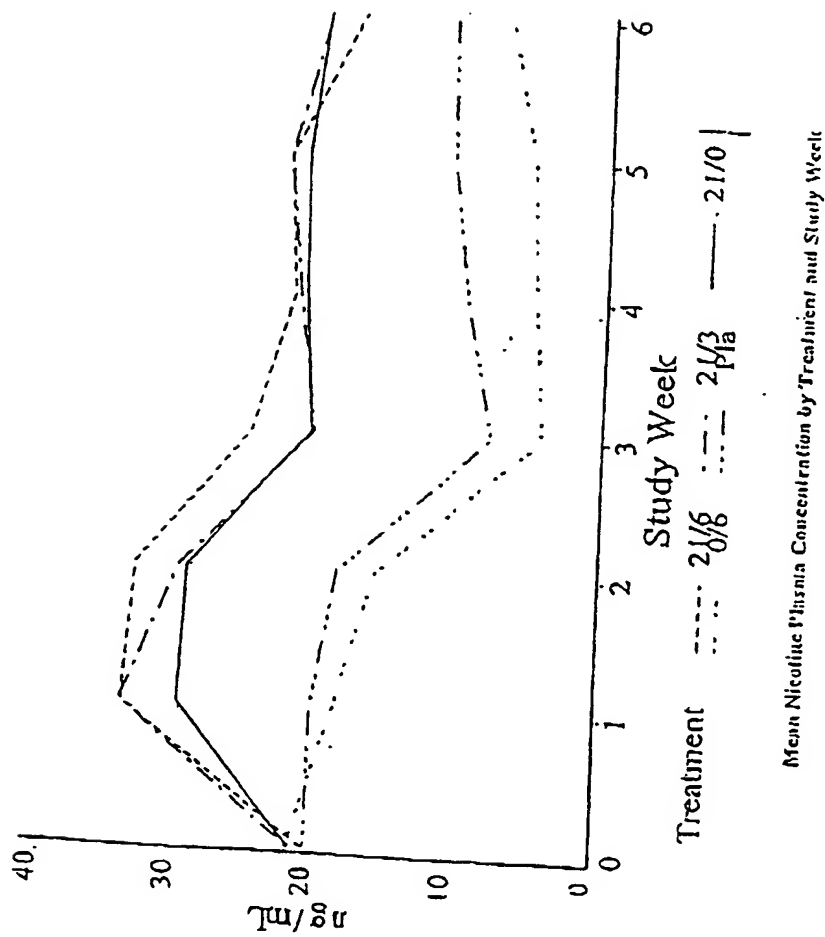
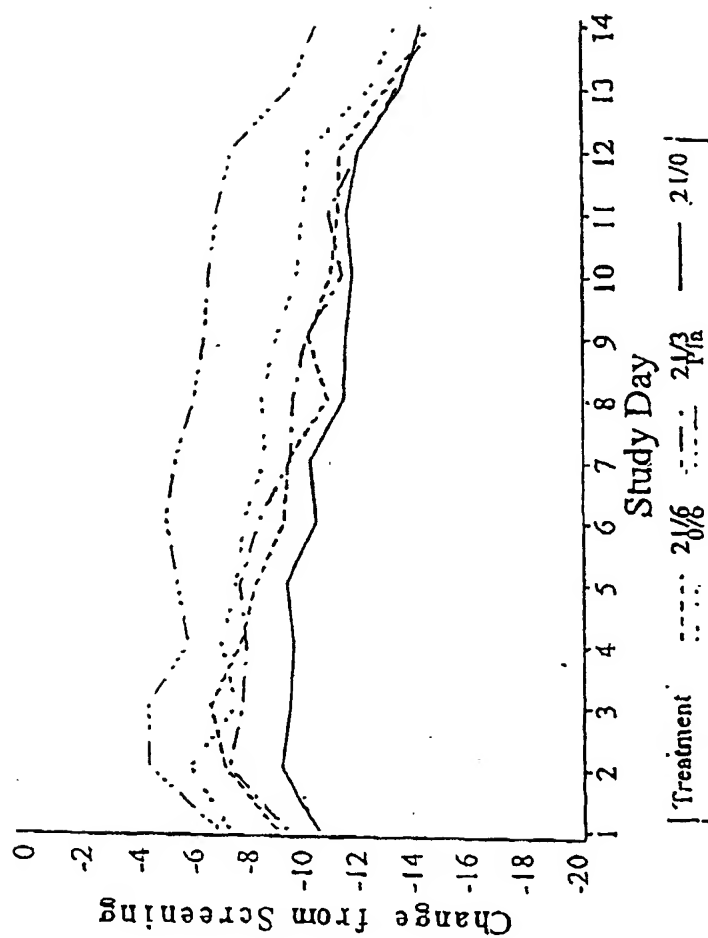


FIGURE 7



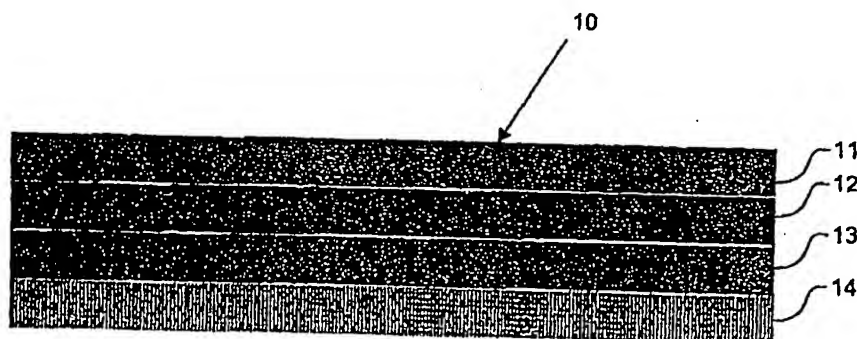
Mean Observed Change in Number of Cigarettes by Treatment and Day

FIGURE 8

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>A61K 9/70, 31/465, 31/137, 31/131,</b> <b>C07D 401/04, C07C 211/27, 211/36</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 00/33812</b> <b>(43) International Publication Date:</b> 15 June 2000 (15.06.00)
<b>(21) International Application Number:</b> PCT/US99/28697 <b>(22) International Filing Date:</b> 7 December 1999 (07.12.99) <b>(30) Priority Data:</b> 60/111,285 7 December 1998 (07.12.98) US <b>(71) Applicant (for all designated States except US):</b> ELAN CORPORATION, PLC [IE/IE]; Lincoln House, Lincoln Place, 2 Dublin (IE). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> MIRANDA, J. [US/US]; Elan Transdermal Technologies, 3250 Commerce Parkway, Miramar, FL 33025 (US). BETLACH, C., J., II [US/US]; Elan Transdermal Technologies, 3250 Commerce Parkway, Miramar, FL 33025 (US). <b>(74) Agents:</b> BEARD, Collen, A. et al.; Jones & Askew, LLP, 2400 Monarch Tower, 3424 Peachtree Road, N.E., Atlanta, GA 30326 (US).	<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). <b>Published</b> <i>With international search report.</i> <b>(88) Date of publication of the international search report:</b> 23 November 2000 (23.11.00)	

**(54) Title:** TRANSDERMAL PATCH FOR DELIVERING VOLATILE LIQUID DRUGS**(57) Abstract**

A transdermal patch for administering a volatile liquid drug, such as nicotine, transdermally to a patient comprising a four-layer laminated composite of: a top drug impermeable backing layer; a pressure sensitive silicone adhesive layer containing the drug; a pressure sensitive acrylic adhesive layer also containing the drug; and a removable siliconized release liner layer. Also disclosed is a method for treating a person for nicotine dependence and particularly for treating a woman for nicotine dependence.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/28697

## A. CLASSIFICATION OF SUBJECT MATTER

A61K9/70, A61K31/465, A61K31/137, A61K31/131, C07D401/04,  
C07C211/27, C07C211/36

According to International Patent Classification (IPC) or to both national classification and IPC <sup>7</sup>

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K, C07D, C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96/40085 A (NOVEN PHARMACEUTICALS, INC.) 19 December 1996, page 8, line 14 - page 9, page 18, line 32 - page 19, line 2, page 19, lines 18-37, examples 2-4, claims 1,3-6, 9,10,17,19-21,24.	1,2, 4,6-8, 10,11, 13
Y	--	3,5
X	WO 93/00058 A (NOVEN PHARMACEUTICALS, INC.) 07 January 1993, page 24, line 9, claims 1-5, 14-19,37-39,53-64,91-93.	1,2, 4,6
Y	--	3,5
Y	US 4717568 A (ECKENHOFF ET AL.)	3,5

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search  
18 April 2000

Date of mailing of the international search report  
27.06.2000

Name and mailing address of the ISA  
European Patent Office, P.O. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+ 31-70) 340-3016

Authorized officer  
KRENN e.h.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/28697

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>05 January 1988, abstract, column 18, lines 25,26. --</p> <p>US 5691365 A (CROOKS ET AL.) 25 November 1997, abstract, column 4, lines 20-29, column 14, lines 50-67, column 16, line 63. --</p>	15-20
X	<p>US 5316759 A (ROSE ET AL.) 31 May 1994, abstract, claims. --</p>	21-26
A	<p>US 5230898 A (HORSTMANN ET AL.) 27 July 1993, the whole document. --</p>	1-26
A	<p>US 5176915 A (HOFFMANN) 05 January 1993, the whole document. ----</p>	1-26

# ANHANG

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

# ANNEX

To the International Search Report to the international Patent Application No.

# ANNEXE

Au rapport de recherche international relatif à la demande de brevet international n°

PCT/US 99/28697 SAE 268121

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This annex lists the patent family members relating to the patent documents cited in the above-mentioned search report. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l' Office.

Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A2 9640085	19-12-1996	AU A1 60289/96	30-12-1996
WO A3 9640085	13-03-1997	CA AA 2223588	19-12-1996
		EP A2 833671	08-04-1998
		IL A0 122484	15-06-1998
		JP T2 11506744	15-06-1999
WO A1 9300058	07-01-1993	AU A1 22689/92	25-01-1993
		AU B2 670033	04-07-1996
		BR A 9206208	22-11-1994
		CA AA 2110914	07-01-1993
		EP A1 591432	13-04-1994
		EP A4 591432	17-05-1995
		FI A 935833	23-12-1993
		FI A0 935833	23-12-1993
		IL A0 102277	14-01-1993
		JP T2 6510279	17-11-1994
		MX A1 9203648	31-01-1995
		NO A0 934523	10-12-1993
		NO A 934523	10-02-1994
		NZ A 243200	25-11-1993
		SG A1 49164	18-05-1998
		US A 5474783	12-12-1995
		US A 5958446	28-09-1999
		US A 5656286	12-08-1997
		US A 6024976	15-02-2000
		ZA A 9209992	23-06-1994
		AT E 99176	15-01-1994
		AU A1 32847/89	22-09-1989
		AU B2 606840	14-02-1991
		CA A1 1338660	22-10-1996
		DE C0 68911920	10-02-1994
		DE T2 68911920	07-07-1994
		DK A0 5494/89	03-11-1989
		DK A 5494/89	29-11-1989
		EP A1 418248	27-03-1991
		EP B1 418248	29-12-1993
		FI A0 904358	04-09-1990
		HK A1 1006285	19-02-1999
		JP T2 3503283	25-07-1991
		JP B2 2659837	30-09-1997
		KR B1 9513461	08-11-1995
		US A 4814168	21-03-1989
		WO A1 8907950	08-09-1989
		US A 4994278	19-02-1991
		US A 4994267	19-02-1991
		US A 5032207	16-07-1991
		US A 5300291	05-04-1994
		US A 5405486	11-04-1995
		US A 5656285	12-08-1997
		US A 5686099	11-11-1997

ANHANG	ANNEX	ANNEXE	
Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.	To the International Search Report to the international Patent Application No.	Au rapport de recherche international relatif à la demande de brevet international n°	
PCT/US 99/28697 SAE 268121			
In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.	This annex lists the patent family members relating to the patent documents cited in the above-mentioned search report. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.	La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l' Office.	
Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
		US A 5719197	17-02-1998
		AT E 122240	15-05-1995
		AU A1 50349/90	13-08-1990
		AU B2 632534	07-01-1993
		CA AA 2044132	12-07-1990
		CA C 2044132	06-05-1997
		DE C0 69019175	14-06-1995
		DE T2 69019175	18-01-1996
		DK T3 379045	09-10-1995
		EP A1 379045	25-07-1990
		EP A1 453505	30-10-1991
		EP A1 634179	18-01-1995
		EP B1 379045	10-05-1995
		ES T3 2071683	01-07-1995
		HK A1 1006155	12-02-1999
		IE B 69048	07-08-1996
		JP T2 4502719	21-05-1992
		JP B4 7093939	11-10-1995
		NL A 9020159	02-01-1991
		PT A 92830	31-07-1990
		PT B 92830	29-12-1995
		WO A1 9007940	26-07-1990
		AU A1 54206/90	21-10-1991
		BR A 9008012	01-12-1992
		DK T3 474647	18-08-1997
		EP B1 474647	05-02-1997
		FI A 924313	25-09-1992
		FI A0 924313	25-09-1992
		WO A1 9114463	03-10-1991
		DE C0 69029909	20-03-1997
		DE T2 69029909	11-09-1997
		EP A1 474647	18-03-1992
		NO A0 923699	24-09-1992
		NO A 923699	01-02-1993
		AU A1 15212/95	01-08-1995
		AU B2 700429	07-01-1999
		BR A 9506470	07-10-1997
		CA AA 2180530	13-07-1995
		CN A 1143318	19-02-1997
		EP A1 737066	16-10-1996
		FI A0 962770	05-07-1996
		FI A 962770	29-08-1996
		HU A0 9601856	30-09-1996
		HU A2 74913	28-03-1997
		IL A0 112269	30-03-1995
		JP T2 9511987	02-12-1997
		NO A0 962833	05-07-1996
		NO A 962833	15-08-1996
		NZ A 278769	27-04-1998



ANHANG	ANNEX	ANNEXE	
Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.	To the International Search Report to the international Patent Application No.	Au rapport de recherche international relatif à la demande de brevet international n°	
PCT/US 99/28697 SAE 268121			
In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.	This annex lists the patent family members relating to the patent documents cited in the above-mentioned search report. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.	La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office.	
Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
	SG	A1 49331	18-05-1998
	WO	A1 9518603	13-07-1995
	ZA	A 9500108	25-03-1996
	CA	AA 2025033	16-03-1991
	AU	A1 20040/92	21-12-1992
	CA	AA 2109099	26-10-1992
	EP	A1 592481	20-04-1994
	SG	A1 43349	17-10-1997
	WO	A1 9219451	12-11-1992
	CA	AA 2126366	22-12-1994
	AT	E 144704	15-11-1996
	AU	A1 14610/92	06-10-1992
	AU	B2 658870	04-05-1995
	AU	A1 28331/95	28-09-1995
	AU	B2 694243	16-07-1998
	CA	AA 2104474	28-08-1992
	DE	C0 69214938	05-12-1996
	DE	T2 69214938	15-05-1997
	DK	T3 573576	01-04-1997
	EP	A1 573576	15-12-1993
	EP	A2 728477	28-08-1996
	EP	A3 728477	11-09-1996
	EP	B1 573576	30-10-1996
	ES	T3 2094906	01-02-1997
	FI	A 933761	26-08-1993
	FI	A0 933761	26-08-1993
	GR	T3 3022708	31-05-1997
	JP	T2 6508820	06-10-1994
	NO	A0 933296	16-09-1993
	NO	A 933296	01-11-1993
	NO	B1 307363	27-03-2000
	SG	A1 49158	18-05-1998
	WO	A1 9215289	17-09-1992
	US	A 5234957	10-08-1993
	US	A 5332576	26-07-1994
	US	A 5446070	29-08-1995
	AU	A1 76722/94	21-03-1995
	CA	AA 2170504	02-03-1995
	WO	A1 9505813	02-03-1995
	WO	A1 9640084	19-12-1996
	WO	A1 9606602	07-03-1996
	AU	A1 60290/96	30-12-1996
	WO	A2 9640086	19-12-1996
	WO	A3 9640086	13-02-1997
	ZA	A 9604735	19-12-1996
	AT	E 148633	15-02-1997
	ES	T3 2097145	01-04-1997
	AU	A1 34168/95	22-03-1996
	CA	AA 2170505	27-02-1996

ANHANG		ANNEX		ANNEXE	
Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.		To the International Search Report to the international Patent Application No.		Au rapport de recherche international relatif à la demande de brevet international n°	
PCT/US 99/28697 SAE 268121					
In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.		This annex lists the patent family members relating to the patent documents cited in the above-mentioned search report. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.		La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l' Office.	
Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication		
US A 4717568	05-01-1988	AU A1 39242/85	26-09-1985		
		AU B2 571400	14-04-1988		
		BE A1 901941	01-07-1985		
		CA A1 1221587	12-05-1987		
		DE A1 3509410	26-09-1985		
		DE C2 3509410	20-03-1997		
		ES A1 540185	16-11-1985		
		ES A5 540185	16-12-1985		
		ES A1 8602388	16-03-1986		
		FR A1 2561103	20-09-1985		
		FR B1 2561103	07-04-1989		
		GB A0 8431661	30-01-1985		
		GB A1 2155787	02-10-1985		
		GB B2 2155787	16-12-1987		
		IT A0 8567263	18-03-1985		
		IT A 1185795	18-11-1987		
		JP A2 60236665	25-11-1985		
		JP B4 6041406	01-06-1994		
		MX A 161579	12-11-1990		
		NL A 8500697	16-10-1985		
		NZ A 210601	08-01-1988		
		US A 4595583	17-06-1986		
		ZA A 8409802	28-08-1985		
		US A 4612186	16-09-1986		
		US A 4624945	25-11-1986		
		US A 4684524	04-08-1987		
		US A 4692336	08-09-1987		
		US A 4717566	05-01-1988		
		US A 4717718	05-01-1988		
		US A 4729793	08-03-1988		
		US A 4772474	20-09-1988		
		US A 4844984	04-07-1989		
		US A 4927633	22-05-1990		
		US A 5000957	19-03-1991		
		AR A1 240399	30-04-1990		
		AU A1 60697/86	12-02-1987		
		AU B2 591511	07-12-1989		
		BE A1 905249	01-12-1986		
		BR A 8603678	10-03-1987		
		CA A1 1278968	15-01-1991		
		DE A1 3625915	19-02-1987		
		DE C2 3625915	24-04-1997		
		ES A1 556303	16-10-1987		
		ES A5 556303	16-11-1987		
		ES A1 8800042	01-01-1988		
		FR A1 2585950	13-02-1987		
		FR B1 2585950	03-03-1989		
		GB A0 8618350	03-09-1986		
		GB A1 2178659	18-02-1987		

ANHANG		ANNEX		ANNEXE	
Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.		To the International Search Report to the international Patent Application No.		Au rapport de recherche international relatif à la demande de brevet international n°	
PCT/US 99/28697 SAE 268121					
In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.		This annex lists the patent family members relating to the patent documents cited in the above-mentioned search report. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.		La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l' Office.	
Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication		
		GB B2 2178659	13-09-1989		
		IT A0 8667641	07-08-1986		
		IT A 1195818	27-10-1988		
		JP A2 62039518	20-02-1987		
		JP B4 8018972	28-02-1996		
		NL A 8601971	02-03-1987		
		NZ A 216991	27-09-1989		
		ZA A 8605914	29-04-1987		
US A 5691365	25-11-1997	none			
US A 5316759	31-05-1994	US A 5574052	12-11-1996		
		US A 5703101	30-12-1997		
		US A 5726190	10-03-1998		
		US A 5861422	19-01-1999		
		US A 5935975	10-08-1999		
		US A 4846199	11-07-1989		
		US A 4945928	07-08-1990		
US A 5230898	27-07-1993	AT E 88911	15-05-1993		
		AU A1 51314/90	04-10-1990		
		AU B2 627283	20-08-1992		
		CA AA 2013050	01-10-1990		
		CA C 2013050	28-04-1998		
		CS A2 9001483	15-10-1991		
		CZ B6 284287	14-10-1998		
		DD A5 293266	29-08-1991		
		DE A1 3910543	11-10-1990		
		DE C2 3910543	07-01-1993		
		DE C0 59001338	09-06-1993		
		DK T3 391172	27-09-1993		
		EP A1 391172	10-10-1990		
		EP B1 391172	05-05-1993		
		ES T3 2055201	16-08-1994		
		FI A0 901556	28-03-1990		
		FI B1 103478	15-07-1999		
		HR A1 930590	30-04-1995		
		HR B1 930590	31-10-1997		
		HU A0 902018	28-08-1990		
		HU A2 54062	28-01-1991		
		HU B 205254	28-04-1992		
		IE B 65520	01-11-1995		
		IL A0 93956	23-12-1990		
		IL A1 93956	31-12-1995		
		JP A2 3027311	05-02-1991		
		JP B2 2552191	06-11-1996		
		KR B1 9607517	05-06-1996		
		NO A0 901458	30-03-1990		
		NO A 901458	02-10-1990		
		NO B 180671	17-02-1997		
		NO C 180671	28-05-1997		
		NZ A 233152	23-12-1991		

ANHANG		ANNEX		ANNEXE	
Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.		To the International Search Report to the international Patent Application No.		Au rapport de recherche international relatif à la demande de brevet international n°	
PCT/US 99/28697 SAE 268121					
In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.		This annex lists the patent family members relating to the patent documents cited in the above-mentioned search report. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.		La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l' Office.	
Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets		Datum der Veröffentlichung Publication date Date de publication	
		PL	B1 163297	31-03-1994	
		PT	A 93621	08-01-1991	
		PT	B 93621	28-06-1996	
		SI	A 9010635	30-06-1998	
		US	A 5702721	30-12-1997	
		YU	A 635/90	31-10-1991	
		ZA	A 9002465	30-01-1991	
US A 5176915	05-01-1993	AT	E 133569	15-02-1996	
		AU	A1 50766/90	01-11-1990	
		AU	B2 622775	16-04-1992	
		CA	AA 2012124	15-09-1990	
		CZ	A3 9001137	17-11-1999	
		DD	A5 296844	19-12-1991	
		DE	A1 3908432	27-09-1990	
		DE	C2 3908432	04-07-1991	
		DE	C0 59010095	14-03-1996	
		DK	T3 387694	24-06-1996	
		EP	A2 387694	19-09-1990	
		EP	A3 387694	28-11-1990	
		EP	B1 387694	31-01-1996	
		ES	T3 2085293	01-06-1996	
		FI	A0 901291	15-03-1990	
		GR	T3 3019786	31-07-1996	
		HR	A1 930666	31-10-1994	
		HR	B1 930666	31-08-1998	
		HU	A0 901423	28-06-1990	
		HU	A2 53814	28-12-1990	
		HU	B 206992	01-03-1993	
		IE	B 74681	30-07-1997	
		IL	A0 93679	23-12-1990	
		JP	A2 3014515	23-01-1991	
		JP	B2 2588039	05-03-1997	
		KR	B1 9513462	08-11-1995	
		NO	A0 901127	09-03-1990	
		NO	A 901127	17-09-1990	
		NZ	A 232896	26-04-1991	
		PH	A 26277	10-04-1992	
		PL	B1 162638	31-12-1993	
		PT	A 93431	07-11-1990	
		PT	B 93431	30-04-1996	
		SI	A 9010494	30-06-1998	
		ZA	A 9001940	28-12-1990	

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**

**THIS PAGE BLANK (USPTO)**